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Serotonin Transporter Polymorphism and Borderline/Antisocial Traits Among Low-Income Young Adults

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Abstract

Objectives—The short allele of the serotonin transporter linked polymorphic region (5HTTLPR) has been associated with anxiety, major depressive disorder, and suicidality. The impulsive self- and other-damaging behaviors seen in borderline personality disorder (BPD) and antisocial personality disorder (APD) also have substantial comorbidity with depression but are associated with more severe environmental stressors. This study tested the hypothesis of an association between the short allele of the 5HTTLPR and borderline or antisocial traits in young adulthood.

Methods—The 5HTTLPR was genotyped among 96 young adults from low- to moderate-income families (62 without and 34 with BPD or APD features). Features of borderline and antisocial personality disorder were assessed with the Structured Clinical interview for Diagnosis (SCID)-Axis II.

Results—The number of short 5HTTLPR alleles was significantly related to incidence of BPD or APD traits, as well as to each set of traits independently. Male gender and quality of care in infancy were also associated with incidence of BPD and APD traits but did not account for the association with the short allele. Depressive disorders were not associated with the short allele in this sample.

Conclusions—Young adults of lower socioeconomic status who carry the short 5HTTLPR allele may be especially vulnerable to developing antisocial or borderline traits by young adulthood.

Keywords

serotonin transporter linked polymorphic region; borderline personality disorder; antisocial personality disorder; maternal care; suicidality

Impulsive self-damaging behaviors constitute the core features of borderline personality disorder while impulsive other-damaging behaviors are criteria for antisocial personality disorder [American Psychiatric Association, 1994]. However, their underlying phenotypic commonalities are acknowledged in that both borderline and antisocial personality disorders are grouped together as part of Cluster B “dramatic/erratic” personality disorders. These two variants of impulse disorders are strongly associated with gender, with males more likely to

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be diagnosed with antisocial disorder and females more likely to be diagnosed with borderline disorder. Therefore, the combined borderline/antisocial symptom phenotype may describe a common core predisposition to engage in disregulated and destructive behaviors when under stress, a phenotype that is expressed somewhat differently by males and females. While both antisocial and self- destructive behaviors have considerable comorbidity with dysphoric symptoms of anxiety and depression, they have also been associated with more adverse life events than anxiety and depression alone [Blantz et al., 1991; Zanarini et al., 1997].

Disruption in the serotonin neurotransmitter system has been linked to suicidal behavior and impulsive aggression toward others by a variety of methods. Low levels of the serotonin metabolite (5-hydroxyindoleacetic acid, 5HIAA) were detected in the cerebrospinal fluid of borderline personality disorder patients and non-suicidal aggressive psychiatric patients [Brown et al., 1982; Stanley et al, 2000]. In one study, low 5HIAA levels were characteristic of impulsive violent offenders [Linnoila et al., 1983]. In addition, tryptophan (the precursor of serotonin) depletion has been reported to increase aggressive behaviors in healthy men [Moeller et al., 1996]. Another determinant of serotonin metabolism, the MAO-A (monoamine oxidase A) enzyme, has been associated with aggressive forms of impulsive behavior. In a large Dutch family study, aggressive and violent behavior was reported in MAO-A deficient men [Brunner et al., 1993]. Mice lacking this enzyme also showed enhanced aggression in adulthood [Cases et al., 1995].

The genetic background of personality disorders, including antisocial and borderline personality disorders (APD and BPD), was assessed by a twin study demonstrating that genetic factors accounted for about 60% of the variance in liability [Torgersen et al., 2000]. Using candidate-gene approach, meta-analyses of data on serotonin-related genes supported the role of the short allele of the serotonin transporter linked polymorphic region (5HTTLPR) as a genetic risk factor for suicide, while other polymorphisms in the serotonin receptor genes were not shown to play a role [Anguelova et al., 2003]. Moreover, Caspi et al. [2003] demonstrated the importance of gene-environment interaction in that stressful life events predicted increased suicidal ideation or attempts among those who had at least one short 5HTTLPR allele but not among those with the long/long genotype. The 5HTTLPR is located in the promoter region of the serotonin transporter gene (SLC6A4) and the short (44 base pair deletion) variant showed reduced transcription activity in reporter gene systems [Heils et al., 1997; Lesch et al., 1996]. Therefore this risk allele may account for reduced serotonin uptake in the serotonergic synapses.

Impulsive aggressive behaviors also show genetic underpinnings. Research involving children and adolescents typically find that both shared rearing environments and genetic factors account for variation in aggressive behaviors [Edelbrock et al., 1995; Miles & Carey, 1997]. A retrospective twin study demonstrated a substantial genetic influence on the risk for conduct disorder, with a heritability estimate of 71% [Slutske et al., 1997]. In a later review Slutske [2001] points out the developmental changes in heritability of antisocial behaviors. In a population-based sample of 6,806 adult twins, Jacobson and colleagues [2002] found that heritability increased from childhood to adolescence and adulthood but the genetic and environmental influences on the development of antisocial behavior were similar for males and females. Demonstrating the potential importance of gene-environment interaction, Caspi et al. [2002] found that maltreated males with the low MAO-A activity genotype were more likely to develop conduct disorder than non-maltreated males with the same genotype.

Consistent with the Caspi et al. [2003] findings that environmental stressors may interact with the presence of the 5HTTLPR short allele to produce depressive symptoms and suicidality, we hypothesized that genetically mediated vulnerability to dysphoric affect may potentiate not only anxiety or depression but also more impulsive self- or other-damaging behaviors. In

particular, genetic vulnerability to such impulsive behaviors may be more evident when environmental conditions are less favorable. Here we examine the contribution of the serotonin transporter promoter polymorphism to antisocial and borderline traits among young adults from low-to moderate-income families.

Method

Participants

Study subjects were 96 young adults aged 18–22 from low-to-moderate income families participating in a study of adolescent-parent relationships. Forty percent of the families (N = 38) had been participating in a longitudinal case-control study of attachment relationships since the first year of the child's life. Longitudinal families were recruited at child age 0–18 months and all families were at or below federal poverty level at intake [Lyons-Ruth et al., 1990]. Fifty-eight additional crossectional families were recruited as part of the young adult follow-up study and matched to the longitudinal sample on socioeconomic status. Among the longitudinal families, 53% had been referred to clinical services during the young adult's infancy for concerns about the quality of care provided and 47% were socioeconomically-matched controls. Problems in early care were further validated by a one-hour observation at home by study clinicians and by laboratory assessments [Lyons-Ruth et al., 1987, 1990, 2004]. The study was conducted in compliance with the Code of Ethics of the World Medical Association and with the requirements of the Hospital Institutional Review Board and the National Institute of Mental Health. All young adults and their mothers provided written informed consent for their participation.

Procedure

Structured Clinical Interviews for Diagnosis (SCID) were administered in the laboratory by trained interviewers to assess borderline and antisocial traits. The SCID yields psychiatric diagnoses for both Axis I and Axis II disorders [First et al., 1997a, 1997b]. Reliability analyses for the SCID have yielded Kappas of .61 for current diagnosis and .68 for lifetime diagnoses. These figures are comparable to other structured diagnostic interviews. Borderline and antisocial traits were coded as present if two or more features of the disorder were endorsed.

Non-invasive sampling and DNA isolation were performed as described elsewhere [Boor et al., 2002], except that Purgene DNA Purification kits (Gentra) were used for DNA isolation. Schleicher & Schuelle IsoCode ID kits were used for samples collected by mail. Genotyping of the 5HTTLPR was performed as described elsewhere [Nemoda et al., 2001]. Genotype frequencies [s/s, s/l, and l/l] did not show significant deviation from the Hardy Weinberg equilibrium ($p = .76$). There was no relation between gender and genotype (χ^2 [2, 896] = 1.03, n.s.), with 61% of males and 66% of females carrying one or more short alleles.

Racial/ethnic characteristics of the sample (N = 96) were as follows: 73% Caucasian; 27% one or two parents African American; no Asian participants. The possibility of spurious association due to sample heterogeneity was assessed by Genomic Control [Devlin & Roeder, 1999], analyzing 40 random marker polymorphisms distributed evenly along the human genome [1–3 markers per chromosome]. No significant association ($p<.05$) was found for the marker polymorphisms with either borderline or antisocial traits. Further analysis of potential racial subpopulations is presented below.

Statistical analyses

SPSS 14.0 for Windows was used for data analysis. Binary logistic regression models were calculated for prediction of borderline/antisocial traits.

Results

Because both antisocial and borderline features are rare and may represent gendered variants of a similar impulsive response to dysphoric affect, in the first set of analyses a single variable indexing the presence of either antisocial or borderline traits was used. Thirty-five percent of young people in the sample displayed borderline or antisocial traits. An initial binary logistic regression analysis was conducted predicting presence of borderline or antisocial traits from male gender, race (Caucasian/African American), and number of short 5HTTLPR alleles [l/l, s/l, s/s]. Number of short 5HTTLPR alleles was significantly associated with presence of APD/BPD traits, Wald = 4.23, df = 1, p < .04, OR = 2.0. Followup contrasts indicated that, with race and gender controlled, the incidence of borderline or antisocial traits was significantly different for young adults with the s/s genotype compared to those with the l/l genotype, Wald = 4.27, d.f. = 1, p = .04, OR = 4.1. Comparison of l/l and s/l genotypes did not reach significance, Wald = 1.34, d.f. = l, p = .25. The data are presented in Table 1.

There was no effect of race on presence of APD/BPD traits, Wald = .36, df = 1, p < .55. Consistent with the literature, with allele frequencies and race controlled, male gender independently conferred significant added risk for APD/BPD traits (primarily APD traits, see below), Wald = 4.24, d.f. = 1, p < .04, OR = 2.6 [28% of females; 47% of males displayed traits]. Given limited statistical power to assess a genotype by race interaction term, data for Caucasian (N = 70) and African-American (N = 26) participants were also analyzed separately. Genotype distribution for Caucasians was 25.7% (l/l), 54.3% (s/l), and 20% (s/s); for African-Americans, 61.5% (l/l), 27% (s/l), and 11.5% (s/s). These descriptive data suggest that African-Americans are less likely to carry the short allele than Caucasians (38.5% vs 74.3%). Furthermore, with gender controlled, the association between the short allele and BPD/APD traits was robust among Caucasians, Wald = 6.00, df = 1, p = .01, OR = 2.8, but there was no similar trend among the small group of African-American families, Wald = .32, p = .57 (see Table 1). Clearly, then, results should be generalized only to Caucasian populations.

Analyses were then conducted for borderline traits and antisocial traits separately in relation to genotype. Among the sample as a whole, borderline traits were associated linearly with the number of short alleles, Wald = 4.23, d.f. = 1, p = .04, OR = 2.2. Antisocial traits were also independently associated with the number of short alleles, Wald = 4.66, d.f. = 1, p = .03, OR = 2.7. In addition, males had a higher incidence of antisocial traits, Wald = 5.46, d.f. = 1, p = .02, OR = 4.0.

The nine features that define borderline personality disorder and the seven features that define antisocial personality disorder are heterogeneous. Given this heterogeneity, the particular BPD and APD features reported were examined to better characterize the phenotype related to the short allele. All those displaying borderline traits exhibited one of the two following behavioral features: two or more forms of impulsive self-damaging behaviors (71%) or intense and unstable relationships (64%). One half reported reactive mood changes. All other features were less frequently noted. Those with antisocial traits also displayed the more impulsive, reactive features of the disorder, with 90% reporting repeated illegal acts, 65% displaying aggressiveness, and 55% exhibiting reckless disregard for safety of self or others. All other features were less frequent. Therefore the phenotype expressed by young adults in this cohort was one of impulsive self- or other-damaging behaviors.

Further logistic regression analysis evaluated whether the association between the 5HTTLPR short allele and APD/BPD traits might be derivative of an association between APD/BPD traits and depressive disorders. Consistent with the lack of a main effect in the Caspi et al. [2003] data, no significant effect for number of short alleles was found on either major depressive disorders or all depressive disorders, MDD Wald = .13, d.f. = 1, n.s.; all depressive disorders

Wald = .52, d.f. = 1, n.s. In addition, entering depressive disorders first into the logistic regression equation did not reduce the significant relation between number of short alleles and prevalence of borderline/antisocial traits, Wald = 4.21, d.f. = 1, p = .04, OR = 2.0. Results were the same for Caucasians only, Wald = 5.30, d.f. = l, p = .02, OR = 2.6.

As noted, 22% of families in the study were referred during the young adult's infancy to clinical services for problems in caregiving. There was no relation between problems in early care and child genotype, Wald = .15, d.f. = 1, n.s. However, problems in early care were related to borderline or antisocial traits, Wald = 6.03, d.f. = 1, p = .01, OR = 3.95. With gender, race, and effects associated with problems in early care accounted for in the model, the effect of the number of short alleles on BPD/APD traits was still robust, both in the whole data set, Wald = 3.98, d.f. = 1, p = .05, OR = 2.0; and among Caucasians only, Wald = 5.43, d.f. = 1, p = .02, OR = 2.7. Given the limited cell sizes, the interaction between genotype and problems in early care could not be tested.

Overall, among low-to- moderate-income families, the odds ratio indicated that the relative risk of antisocial or borderline traits was increased by a factor of 2 for each short allele in the genotype. Among individuals possessing only short alleles 53% reported borderline or antisocial traits by young adulthood, while 38% (s/l) and 24% (l/l) did so in the presence of one or no short alleles. For Caucasians only, corresponding rates were 64%, 39%, and 22% (see data in Table 1).

Discussion

These results suggest a relation between the short 5HTTLPR allele and borderline and antisocial traits. A recent case-control study did not find association with the 5HTTLPR or the A/G SNP within this repeat sequence among individuals meeting full criteria for borderline personality disorder (Ni et al., 2006). Only the 10-repeat allele of the intron 2 VNTR and its combination with the short 5HTTLPR allele showed significant association with the full syndrome of BPD. The present results suggest that the short 5HTTLPR allele may confer a broader endophenotype for impulsive self- and other-damaging behaviors that, in turn, contributes to the more complex APD and BPD disorders described in the DSM-IV.

Limitations of the study include the relatively small sample size and the predominantly low-income nature of the sample. The main effect of the short allele found here may represent a gene-environment interaction in that the short form of the 5HTTLPR polymorphism may be related to internalizing symptoms of depression and anxiety in more advantaged environments, while in more stressful low-income environments genetic vulnerability may be expressed through more impulsive self- and other-damaging behaviors, consistent with the relation between BPD/APD and cumulative family adversity [Blanz et al., 1991; Zanarini et al., 1997]. Given demonstrations of environmental potentiation of genetic effects on stress-responsiveness in animal models [Francis et al., 1999; Barr et al., 2003], future work should include careful assessment of environmental stressors as potential regulators of the relation observed here.

The consistency of the genetic association with BPD/APD traits over gender, symptom type, and quality of early care points to the potential stability of the finding for Caucasian populations. Further work is in progress to increase sample size, assess parental genotype, and test the possibility of gene-environment interaction.

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Table 1

Serotonin Transporter Genotype Frequencies among Young Adults with and without Borderline or Antisocial Traits

Borderline or Antisocial Traits		Serotonin Transporter Genotype		
	n	l/l genotype	s/l genotype	s/s genotype
Absent	62	.42 (26)	.45 (28)	.13 (8)
Caucasian	42	.33 (14)	.54 (23)	.11 (5)
African American	20	.60 (12)	.25 (5)	.15 (3)
Present	34	.24 (8)	.50 (17)	.27 (9)
Caucasian	28	.14 (4)	.53 (15)	.32 (9)
African American	6	.66 (4)	.33 (2)	0
Total	96	34	45	17